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10/542,839	12/13/2005	Tetsuo Kojima	14875-148US1 C1-A0231P-US	8994

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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
06/03/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/542,839	KOJIMA, TETSUO	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10,13-15 and 18-26* is/are pending in the application.

4a) Of the above claim(s) *10 and 18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/17/09 has been entered.

2. Claims 1-7, 10, 13-15, and 18-26 are all the pending claims for this application.

3. Claims 8, 9, 11, 12, 16 and 17 were cancelled, Claims 1, 2, and 5-7 were amended, and new Claims 19-26 were added in the Response of 3/17/09.

4. Newly submitted Claims 19-26 are directed to an invention that is distinct from the invention originally claimed for the following reasons:

The originally elected claims are drawn to bacterial phage -based methods of infecting bacterial host cells in order to obtain resultant phage libraries where each phage expresses an antibody heavy chain and light chain and selecting the phage on antigen binding specificity.

Now Applicants have introduced new Claims 19-26 which are drawn to using expression vector-based methods of transfecting eukaryotic host cells in order to obtain resultant host cells where each host cell expresses an antibody heavy chain and light chain and selecting the host cells on antigen binding specificity.

The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed require different material reagents and different process steps. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 19-26 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. Claims 10 and 18-26 are withdrawn from examination.

6. Claims 1-7 and 13-15 are all the pending claims under examination.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

7. The rejection of Claims 1-7 and 13-15 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained.

The rejection was set forth in the Office Action of 6/20/08 as follows:

"Nature of the Invention/ Skill in the Art

Claims 1 and 3-6 are interpreted as being drawn to a method of screening for commonly shared antibody light chains which correspond to two or more types of different antibody heavy chains where in the initial step host cells "secreting" the heavy chain against a target antigen are provided, then a phage library encoding a plurality of different light chains is introduced into the host cells in order to secrete a library of phage particles presenting the heavy chain and a light chain, where the library is screened for specific binding to the target antigen, then where the screened library is introduced into host cells "secreting" a second heavy chain that binds to a different antigen than the first antigen in order to secrete a library of phage particles presenting the second heavy chain and a light chain, and finally where the phage libraries produced from the second introducing step are selected for binding to the second target antigen (Claim 1), where the first and second heavy chains are Fd (Claim 3), the host is E. coli (Claim 4), the steps are performed twice or more (Claim 5) and the method further comprises introducing the second screened phage particle library into a host "secreting" a third heavy chain that binds to a third and different antigen from the first and second antigens and selecting the phage particle library that bind to the third antigen (Claim 6).

Claims 2, 7 and 13-15 are interpreted as being drawn to a method of screening for commonly shared antibody light chains which correspond to two or more antibody heavy chains of different amino acid sequence where in the initial step host cells "secreting" the heavy chain against a target antigen are provided, then a phage library encoding a plurality of different light chains is introduced into the host cells in order to secrete a library of phage particles presenting the heavy chain and a light chain, where the library is screened for specific binding to the target antigen, then where the screened library is introduced into host cells "secreting" a second heavy chain comprising a different amino acid sequence than the first heavy chain in order to secrete a library of phage particles presenting the second heavy chain and a light chain, and finally where the phage libraries produced from the second introducing step are selected for binding to the target antigen recognized by the second antibody (Claim 2), and the method further comprises introducing the second screened phage particle library into a host "secreting" a third heavy chain having an amino acid sequence different from the first and second heavy chain and selecting the phage particle library that bind to the antigen recognized by the third heavy chain (Claim 7), where the first and second heavy chains are Fd (Claim 13), the host is E. coli (Claim 14), and the steps are performed twice or more (Claim 15).

The relative skill in the art required to practice the invention is a molecular immunologist with a background in phage display library production and screening for recombinant antibodies.

Disclosure in the Specification

The specification generally teaches methods of screening for commonly shared light chains which correspond to two or more types of different antibody heavy chains. Hosts which secrete heavy chains of antibodies that bind to desired antigens must be obtained first. Two types of hosts that each secretes a heavy chain corresponding to one of the two types of desired antigens are necessary for generating a BsAb, three types are necessary for a tri-specific antibody, and four types are necessary for a tetra-specific antibody. To obtain these hosts, the specification teaches producing antibody-producing cells from mammals (p. 7, lines 9-28). Host cells that secrete antibody heavy chains may secrete full-length antibody heavy chains or partial fragments (p. 10, lines 21-23). A gene portion that encodes a desired antibody heavy chain is introduced into an expression vector that is suitable for expression in appropriate host cells. Host cells are preferably bacteria that can be infected by phages, particularly gram negative bacteria (p. 10, lines 30-35). Phage particles contemplated by the invention are listed on p. 12, lines 20-23.

The following examples are provided for performing method steps:

Eukaryotic host cell/ expression vector (working example): the specification at p. 13, lines 2-16 incorporates by reference the disclosure from WO 95/15393 for constructing antibody libraries using eukaryotic cells that present antibodies on their cell surfaces. An expression vector carrying a gene that encodes a desired heavy chain (for example, Fd), and is linked downstream of a promoter appropriate for its expression and a signal sequence which enables the secretion of the heavy chain, is introduced into eukaryotic host cells. Expression vectors are constructed with light chain-encoding genes linked to a transmembrane region-encoding sequence and inserted downstream of an appropriate promoter, so that the light chains will be displayed on cell surfaces when expressed. By introducing light chain expression vectors into the aforementioned heavy chain-secreting host cells, host cells which *express on their cell surfaces* antibodies that bind to a desired antigen can be selected. The displayed antibody is a Fab fragment when Fd is used as the heavy chain and those comprising VL and CL are used as the light chains.

Bacterial host cell/ phage library (prophetic example): A light chain library is introduced into the E. coli host which expresses an antibody A heavy chain (for example, Fd), and by infecting the host with helper phages, a phage library, which presents *on their surfaces* antibodies comprising an antibody A heavy chain and various light chains (Fab when the heavy chain is Fd and the light chain comprises VL and CL) as fusion proteins (p. 12, line 30- p. 13, line 1).

The specification is enabling for using a host cell system compatible with a phage library being introduced into the host cell such as a bacterium which produces phage particles expressing an assembled antibody heavy and light chain on the particle surface after following the method steps. The specification is not enabling for introducing a phage library into just any host cell much less where the host cell is a eukaryotic cell. The specification is not enabling for any host cell having the ability to "secrete" an antibody heavy chain much less where a bacterial host cell secretes the first or second or third antibody heavy chain. The claims encompass any host cell a) having the ability to secrete an antibody heavy chain and b) capable of being infected with a phage particle library whereas the specification is only enabling for using phage particles to infect a bacterium where at most the resultant, selected phage particle library also expresses the heavy chain and light on the surface. The specification is not enabling for the genus of host cells having all of the properties of the instant claimed method.

Prior Art Status: E. coli host cells express and transport antibody fragments comprising a bacterial signal peptide into the periplasmic space

The prior art does not recognize bacterial cells, more specifically E. coli, as being capable of secreting antibody fragments absent the fragment being engineered to have a bacterial signal peptide. As reviewed by Kipriyanov et al. (Molec. Biol. 12: pp. 173-201 (1999)) E. coli can express antibody fragments such as Fab, Fv and scFv into the periplasm. "Periplasmic expression has permitted the functional testing of a wide variety of antibody fragments with different antigen binding specificities. The antibody fragments are usually correctly processed in the periplasm, they contain intramolecular disulfide bonds and are soluble. However, the high-level expression of a recombinant protein with a bacterial signal sequence in E.coli often results in the accumulation of insoluble antibody fragments after transport to the periplasm, presumably via the aggregation of a folding intermediate"...and "high protein concentrations of the secreted antibody fragment in the periplasmic space would favor the formation of insoluble aggregates over correct folding."

Thus one of skill in the art could not even predict that any antibody heavy chain could be "secreted" by any host cell much less a bacterium and that the same host cell could be infected with a library of phage particles encoding any random antibody light chain where the host cell then produced a phage particle expressing on its cell surface an assembled heavy and light chain antibody with specific antigen binding ability or at least antigen binding ability for the recognized antigen of the heavy chain. Because of the lack of working examples in the specification for the scope of host cells encompassed by the instant method claims, the ordinary artisan would be forced into undue trial and error experimentation to practice using the method based on the written description in the specification alone.

Applicants allegations on pp. 8-11 of the Response of 3/17/09 have been considered and are persuasive in part as regards point (1) (a phage library in any kind of host cell) on p. 9 but unpersuasive as regards point (2) (making the method work in bacterial cells) on p. 9.

As regards *point (1)*, Applicants allege that in amending the generic claims to require that the host is bacterial in order to be infected with a phage library, point one (1) of the rejection is overcome. The examiner concurs that this aspect of the rejection is overcome.

As regards *point (2)*, Applicants allege "the observation that recombinant proteins in E. coli can aggregate when expressed at high levels is largely irrelevant to a screening method, in which high level expression of individual library members is not needed. Use of phage libraries in bacterial hosts to screen for two-chain antibodies is well known in the art, so techniques for avoiding aggregation of the secreted chain--if it is ever an issue--are apparently known. See, for example, Griffiths et al., The EMBO Journal 13:3245-3260 (1994))"; Kipryanov recognized that these methods work; and "The fact that, as Kipryanov goes on to note, high level expression of a recombinant protein in E. coli (e.g., for large-scale production of a desired antibody) may result in aggregation is irrelevant to the question of whether lower levels that are adequate for screening purposes would work."

Response to Arguments

Applicants have not even provided a copy of the Griffiths reference with their filed Response of 3/17/09 thus precluding the examiner from verifying the reference content.

As regards the examiner's previous reference to Kipryanov, it is noted that Applicants have conveniently edited the reference interpretation in favor of their position, which is to wholly ignore it's teaching, namely, that in order for this method to work in a bacterium, where the bacterial host cells are "***secreting*** the heavy chain of an antibody" as instantly claimed, the protein would be required to comprise a bacterial signal peptide in order to even be expressed in the periplasmic space much less "secreted." Elements (a) and (d) in each of the generic claims 1 and 2 require protein secretion from a bacterial host.

As regards Applicants assertion that screening antibodies does not require the same extent of expressed protein as required for large-scale production, the examiner finds this to be wholly irrelevant to the instant rejection. Zauderer et al. (US 20080167193; published 7/10/08; priority to 11/14/01) substantiate the examiner's position stating:

"Immunoglobulin libraries constructed in bacteriophage may derive from antibody producing cells of naive or specifically immunized individuals and could, in principle, include new and diverse pairings of human immunoglobulin heavy and light chains. Although this strategy does not suffer from an intrinsic repertoire limitation, it requires that complementarity determining regions (CDRs) of the expressed immunoglobulin fragment be synthesized and fold properly in bacterial cells. Many antigen binding regions, however, are difficult to assemble correctly as a fusion protein in bacterial cells. In addition, the protein will not undergo normal eukaryotic post-translational modifications. As a result, this method imposes a different selective filter on the antibody specificities that can be obtained" [0013],

and

"Assays for expression in bacterial hosts are often impeded, however, because the protein may not be sufficiently expressed in bacterial hosts, it may be expressed in the wrong conformation, and it may not be processed, and/or transported as it would in a eukaryotic system. Many of these problems have been encountered in attempts to produce immunoglobulin molecules in bacterial hosts…" [0016].

The rejection is maintained.

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
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